Organic LETTERS

Letter

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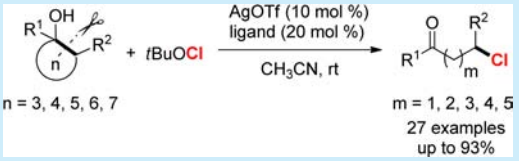
Regioselective Synthesis of Carbonyl-Containing Alkyl Chlorides via Silver-Catalyzed Ring-Opening Chlorination of Cycloalkanols

Feng-Qing Huang, Jian Xie, Jian-Guo Sun, Yue-Wei Wang, Xin Dong, Lian-Wen Qi,* and Bo Zhang*

State Key Laboratory of Natural Medicines, China Pharmaceutical University, 24 Tongjia Xiang, Nanjing 210009, China

Supporting Information

ABSTRACT: A novel and regioselective approach to carbonyl-containing alkyl chlorides via silver-catalyzed ring-opening chlorination of cycloalkanols is reported. Concurrent C(sp^3)−C(sp^3) bond cleavage and C(sp^3)−Cl bond formation efficiently occur with good yields under mild conditions, and the chlorinated products are readily transformed into other useful synthetic intermediates and drugs. The reaction features complete regioselectivity, high efficiency, and excellent practicality.



Alkyl chlorides are a highly important and valuable class of compounds, which have gained considerable attention from the synthetic community because of their wide application as versatile building blocks and synthetic intermediates in natural product and drug synthesis.[1] It is estimated that more than 70% of all pharmaceutical products possess chlorine or are manufactured using chlorine. In addition, numerous natural products contain chlorine and many of them show excellent bioactivity such as antibiotic or cytotoxic activity.[2] In light of the importance of this class of compound, there is continuing interest in the development of synthetic methods for C(sp^3)−Cl bond construction. In general, the alkyl chlorides are prepared from their corresponding alcohols,[3] carboxylic acids,[4] and diazo compounds.[5] However, these precursors are not sometimes easy to obtain. Other alternative and complementary approaches to alkyl chlorides rely on chlorination of olefins[6] or alkynes.[7]

From the point of view of atom and step economy, the direct chlorination of inert chemical bonds such as C(sp^3)−H bonds and C(sp^3)−C(sp^3) bonds is the most straightforward and attractive approach for C(sp^3)−Cl bond formation because of their abundance in organic compounds. Although direct chlorination of unreactive alkanes can generate alkyl chlorides, this route usually suffers from some obvious limitations including poor regioselectivity and harsh reaction conditions.[8] In recent years, palladium-catalyzed directed C(sp^3)−H activation methods for the preparation of alkyl chlorides have emerged as an efficient strategy for the regioselective construction of a C(sp^3)−Cl bond.[9] However, the C(sp^3)−Cl bond formation is limited to benzylic C−H bonds of 8-methyl quinoline,[9a] 1°-C(sp^3)−H bonds of *N*-methoxy amide,[9b] 2-*tert*-butylpyridine,[9c] and *S*-methyl-*S*-2-pyridyl-sulfoximine.[9d] Therefore, the development of novel and efficient methods for the regioselective construction of a C(sp^3)−Cl bond remains fascinating and challenging at the same time.

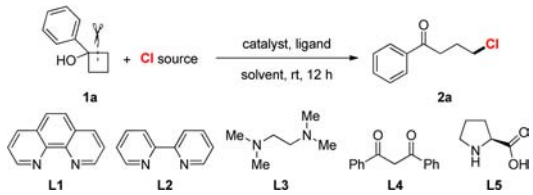
Cycloalkanols are important and versatile compounds, which have found widespread applications in organic synthesis.[10,11] Recently, transition-metal-catalyzed[12] and radical-mediated[13] ring-opening cross-coupling of cycloalkanols have emerged as powerful tools for the regioselective synthesis of *β*- and *γ*-functionalized ketones.[14] Encouraged by these successful examples, we became interested in constructing carbonyl-containing alkyl chlorides from cycloalkanols via the ring-opening cross-coupling strategy.[15] It is important to note that carbonyl-containing alkyl chlorides frequently serve as key synthetic intermediates for the synthesis of bioactive molecules.[16] Herein, we describe a novel, silver-catalyzed direct chlorination of cycloalkanols via C(sp^3)−C(sp^3) bond cleavage producing carbonyl-containing alkyl chlorides. The reaction proceeds efficiently with complete regioselectivity. A variety of valuable *β*-, *γ*-, *δ*-, *ε*-, and *ζ*-chlorinated ketones were readily prepared in moderate to excellent yields under mild conditions.

As the Cl source, we used commercially available and stable *tert*-butyl hypochlorite (*t*BuOCl), and initial studies were conducted on readily prepared cyclobutanol **1a**. We first screened various Ag salts as catalysts in DCM at room temperature for 12 h under a nitrogen atmosphere. Unfortunately, the targeted product **2a** was not formed in the presence of AgF, AgSCN, $AgNO_3$, $AgBF_4$, or AgOTf (Table 1, entry 1). Because ligands play a key role in various transition-metal-catalyzed reactions, we next screened a range of ligands **L1**−**L5** in the presence of AgOTf as a catalyst (Table 1, entries 2−6). The yield of **2a** was significantly improved to 82% by employing 1,10-phenanthroline **L1** as a ligand. Encouraged by this result, we further optimized the reaction conditions. A series of Ag salts, such as AgF, AgSCN, $AgNO_3$, and $AgBF_4$, were tested under the same conditions, affording **2a** in 49−75% yields (Table 1, entries 7−10). These results indicate that AgOTf performed better. In addition, the reaction did not work well in the presence of Fe and Cu salts as catalysts (Table 1, entries 11 and 12). Alternative Cl reagents, such as TsCl, NaCl, nBu_4NCl, and NCS, did not provide the desired product **2a** (Table 1, entries 13−16). Solvent effects were investigated, and we found that CH_3CN is the best solvent for the trans-

Received: December 24, 2015
Published: February 3, 2016

DOI: 10.1021/acs.orglett.5b03649
Org. Lett. 2016, 18, 684−687

Table 1. Optimization of Reaction Conditions[a]



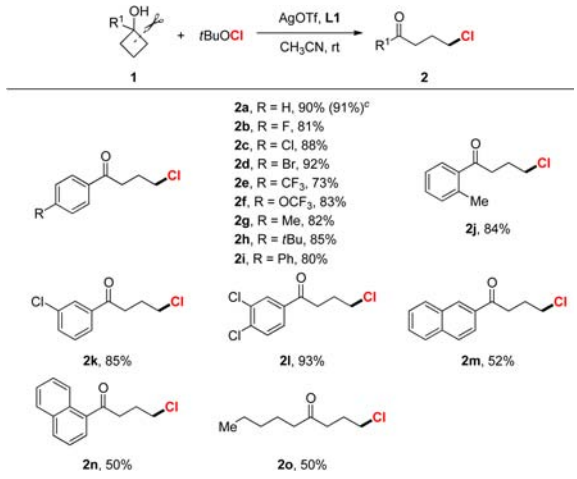
entry	catalyst	ligand	Cl source	solvent	yield[b] (%)
1[c]	AgX	none	*t*BuOCl	DCM	0
2	AgOTf	**L1**	*t*BuOCl	DCM	82
3	AgOTf	**L2**	*t*BuOCl	DCM	72
4	AgOTf	**L3**	*t*BuOCl	DCM	trace
5	AgOTf	**L4**	*t*BuOCl	DCM	trace
6	AgOTf	**L5**	*t*BuOCl	DCM	trace
7	AgF	**L1**	*t*BuOCl	DCM	61
8	AgSCN	**L1**	*t*BuOCl	DCM	49
9	$AgNO_3$	**L1**	*t*BuOCl	DCM	65
10	$AgBF_4$	**L1**	*t*BuOCl	DCM	75
11	$Fe(OTf)_2$	**L1**	*t*BuOCl	DCM	trace
12	$2[CuOTf]\cdot C_6H_6$	**L1**	*t*BuOCl	DCM	trace
13	AgOTf	**L1**	TsCl	DCM	0
14	AgOTf	**L1**	NaCl	DCM	0
15	AgOTf	**L1**	nBu_4NCl	DCM	0
16	AgOTf	**L1**	NCS	DCM	0
17	AgOTf	**L1**	*t*BuOCl	CH_3CN	88
18	AgOTf	**L1**	*t*BuOCl	THF	0
19	AgOTf	**L1**	*t*BuOCl	DCE	74
20[d]	AgOTf	**L1**	*t*BuOCl	CH_3CN	72
21[e]	**AgOTf**	**L1**	***t*BuOCl**	**CH_3CN**	**90**
22[e,f]	AgOTf	**L1**	*t*BuOCl	CH_3CN	39
23	none	**L1**	*t*BuOCl	CH_3CN	trace

[a]Reaction conditions: **1a** (0.3 mmol), catalyst (10 mol %), ligand (20 mol %), and *t*BuOCl (0.6 mmol) in solvent (2.0 mL) at room temperature under N_2 for 12 h. [b]Isolated yields. [c]Using AgF, AgSCN, $AgNO_3$, $AgBF_4$, or AgOTf as a catalyst. [d]Using 5 mol % of AgOTf and 10 mol % of **L1**. [e]The reaction was conducted for 6 h. [f]The reaction was conducted under air.

formation (Table 1, entries 16−18). Lowering the catalyst and ligand loading decreased the yield to 72% (Table 1, entry 20). When the reaction was performed for 6 h, the yield was not affected (Table 1, entry 21). When the reaction was carried out under air, **2a** was obtained in 39% yield (Table 1, entry 22). The reaction did not proceed well in the absence of a silver catalyst, which confirmed the catalytic effect of silver salt (Table 1, entry 23).

With optimized reaction conditions in hand, the scope and limitations of this process were investigated. A variety of cyclobutanols bearing different substituents were tested, and the results are listed in Scheme 1. All of the reactions achieved full conversion within 6 h at room temperature. Aryl-substituted cyclobutanols containing electron-withdrawing or -donating substituents at the *para* position of the benzene ring were good substrates to afford the desired products **2b−2i** in good to excellent yields (73−92%). The substituent positions did not affect the efficiency of the reaction to a large extent (see **2j−2l**). The naphthyl derivatives underwent the transformation smoothly to generate the corresponding products in moderate yields (see **2m** and **2n**). Notably, alkyl-substituted cyclobutanol **1o** was found to be compatible under optimized conditions, leading to the desired product **2o** in 50% yield. To show the

Scheme 1. Various γ-Chlorinated Ketones Prepared[a,b]

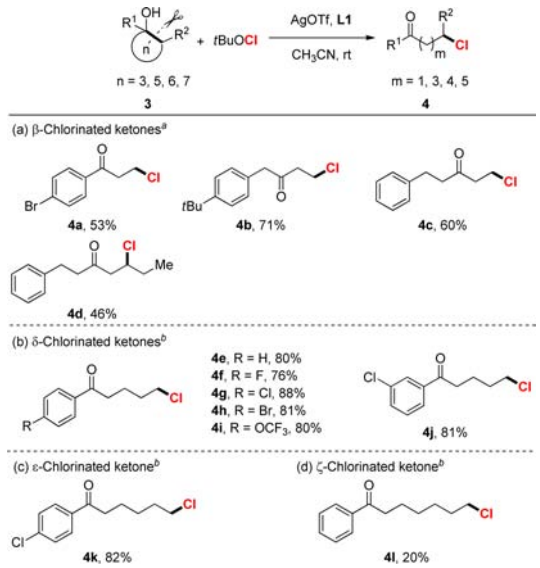


[a]Reaction conditions: **1a** (0.3 mmol), AgOTf (10 mol %), **L1** (20 mol %), and *t*BuOCl (0.6 mmol) in CH_3CN (2.0 mL) at room temperature under N_2 for 6 h. [b]Isolated yields. [c]1.66 g of **2a** prepared.

practicality of the method, we ran a preparative scale reaction with **1a** to produce **2a** in 91% yield (1.66 g).

We next investigated the reaction of cyclopropanols with *t*BuOCl. Various β-chlorinated ketones could be readily prepared by using the ring-opening strategy (Scheme 2a).

Scheme 2. Various β-, δ-, ε-, and ζ-Chlorinated Ketones Prepared



[a]Reaction conditions: **1a** (0.3 mmol), AgOTf (10 mol %), **L1** (20 mol %), and *t*BuOCl (0.6 mmol) in solvent (2.0 mL) at room temperature under N_2 for 6 h. [b]Reaction conditions: **1a** (0.3 mmol), AgOTf (10 mol %), **L1** (20 mol %), and *t*BuOCl (0.9 mmol) in solvent (2.0 mL) at room temperature under N_2 for 48 h. [c]Isolated yields.

Compared to cyclobutanols, cyclopropanols provided lower yields due to some side reactions. When 1-aryl-substituted cyclopropanol **3a** was used as the substrate, the targeted product **4a** was obtained in 53% yield. Moreover, alkyl-substituted cyclopropanols were successfully converted to the corresponding products in good yields (see **4b** and **4c**). We also successfully tested a disubstituted cyclopropanol **3d** and

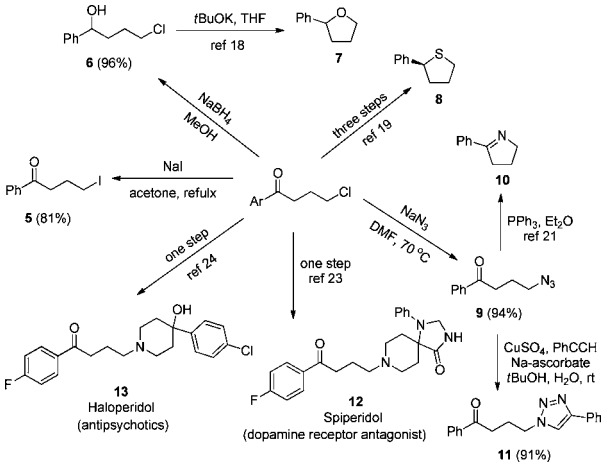
DOI: 10.1021/acs.orglett.5b03649
Org. Lett. 2016, 18, 684−687

isolated β-chlorinated ketone **4d** in 46% yield with complete regiocontrol.

To explore the scope of the reaction further, we turned our attention to the ring-opening chlorination of less strained cyclopentanols. The δ-chlorinated ketone **4e** could be obtained in 80% yield with full conversion by using 3.0 equiv of *t*BuOCl in CH_3CN at room temperature for 48 h (Scheme 2b). Under these conditions, various aryl-substituted cyclopentanols containing different groups proceeded efficiently and afforded the corresponding products **4f**–**4j** in good to excellent yields with complete conversion. Finally, we showed that the ring-opening chlorination reaction could also be applied to the synthesis of ε-chlorinated ketones. For instance, ε-chlorinated ketone **4k** was prepared in 82% yield with 100% conversion from cyclohexanol **3k** (Scheme 2c). However, the reaction conducted on cycloheptanol **4l** provided a low yield due to the formation of some byproducts (Scheme 2d).

Chlorine-substituted ketones are useful precursors for further functionalization and readily provide other valuable synthetic intermediates e.g., via halogen-exchange reaction, nucleophilic substitution, or carbonyl reduction. As a representative, a variety of transformations are displayed by using γ-chlorinated ketones as starting materials (Scheme 3). Alkyl iodide **5** was

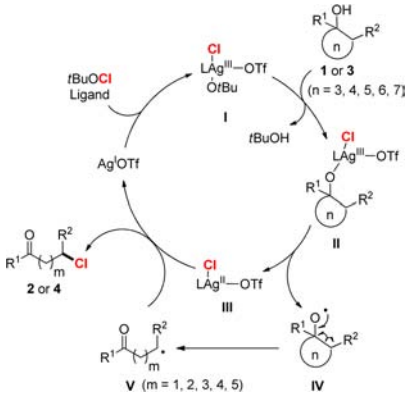
Scheme 3. Transformations of γ-Chlorinated Ketones



readily prepared in 81% yield from **2a** via halogen-exchange reaction.[17] Carbonyl reduction in **2a** with $NaBH_4$ in MeOH provided alcohol **6** in 96% yield, which could be transformed into valuable 2-phenyltetrahydrofuran **7**.[18] Moreover, chiral tetrahydrothiophene **8** could be obtained in three steps from **2a** according to the literature.[19] **2a** was easily converted to alkyl azide **9** in 94% yield by using NaN_3/DMF at 70 °C.[20] 2-Phenyl-1-pyrroline **10** could be synthesized by the reaction of **9** with PPh_3/Et_2O via iminophosphorane as the intermediate.[21] As expected, **9** was a suitable substrate for a click reaction, providing triazole **11** in 91% yield.[22] Notably, the current approach provides many opportunities for application to drug and bioactive molecule synthesis. For example, spiperidol **12** (dopamine receptor antagonist) and haloperidol **13** (antipsychotics) could be readily prepared in one step from **2b** and corresponding amines according to the reported procedure.[23,24]

Preliminary mechanistic studies revealed that the ring-opening chlorination of cycloalkanols seems to proceed through a radical process. To obtain additional support for this mechanism, the reaction of **1a** was conducted under the standard conditions in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical scavenger. As expected, addition of BHT or TEMPO completely suppressed formation of **2a**. On the basis of these experiments and previous reports,[13] a plausible reaction mechanism is proposed in Scheme 4. First,

Scheme 4. Proposed Reaction Mechanism



AgOTf is oxidized by *t*BuOCl to generate the Ag(III) species **I**,[25] which undergoes ligand exchange and coordinates with cycloalkanols to afford the intermediate **II**. Subsequently, homolysis of intermediate **II** provides the Ag(II) species **III** and oxygen-centered radical **IV**, which undergoes rearrangement to give the alkyl radical **V**. Finally, **V** reacts with the Ag(II) species **III** to form the products.[4d] This process allows the regeneration of the Ag catalyst.

In summary, we have presented a novel and efficient approach for the preparation of carbonyl-containing alkyl chlorides via silver-catalyzed ring-opening chlorination of cycloalkanols. The transformation uses commercially available and stable *t*BuOCl as the Cl source. Reactions are very easy to conduct, and a wide range of β-, γ-, δ-, ε-, and even ζ-chlorinated ketones are obtained in moderate to excellent yields. The synthetic value of chlorinated products has been documented by a series of chemical transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03649.

Experimental details and characterization data for the products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zb3981444@cpu.edu.cn.
*E-mail: Qilw@cpu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to a Start-up Grant from China Pharmaceutical University for financial support of this work.

DOI: 10.1021/acs.orglett.5b03649
Org. Lett. 2016, 18, 684–687

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DOI: 10.1021/acs.orglett.5b03649
Org. Lett. 2016, 18, 684–687